IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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DECLARATION UNDER 37 C.F.R. 1.132 Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	CALD-005
	First Named Inventor	CALDWELL, LARRY
	Confirmation Number	3760
	Application Number	10/029,408
	Filing Date	December 26, 2001
	Group Art Unit	1618
	Examiner Name	OH, SIMON J.
	Title:	METHODS AND COMPOSITIONS FOR TREATING CARPAL TUNNEL SYNDROME

Dear Sir:

I, Bradley Galer, am an inventor of the subject matter claimed in the patent application identified above. A copy of my C.V. which demonstrates that I am qualified to speak on the level of one of skill in the art is already of record in this application.

I hereby declare as follows:

1. I have read the Office Action dated **February 27, 2007** that issued in the above referenced case. I have also read Petrus (U.S. Patent No. 6,399,093), the reference cited in support of the rejections made by the Office.

2. Petrus characterizes musculoskeletal disorders as follows:

> The musculoskeletal system consists of bones, muscles and joints. Ten percent of medical visits to physicians are for disorders of the musculoskeletal system. Musculoskeletal disorder include: sprains, strains, tendinitis, tenosynovitis, fibromyalgia, osteoarthritis, rheumatoid arthritis, gout, pseudogout (calcium pyrophosphate deposition disease), polymyalgia rheumatica, bursitis, acute and chronic back pain and osteoporosis, which interfere with the normal performance of activities of daily living. Injuries include sprains, strains and tears of ligaments, tendons, muscles and cartilage damage. Pain is the most common symptom and is frequently caused by injury or inflammation. Besides pain, other symptoms such as stiffness, tenderness, weakness and swelling or deformity of affected parts are manifestations of musculoskeletal disorders. Sports injuries are a significant cause of musculoskeletal disorders resulting in pain, strain, sprains, stiffness and leg cramps.

3. In contrast to musculoskeletal disorders which are the target pathology in the Petrus reference, Carpal Tunnel Syndrome is not a species of musculoskeletal disorders. Rather, Carpal Tunnel Syndrome is a condition whose symptoms are caused by a disturbance of median nerve function in the wrist as the nerve passes through the carpal tunnel. As such, the pain and symptoms caused by Carpal Tunnel Syndrome do not arise from the musculoskeletal system. Instead, the pain, parasthesia, and dysesthesia arise from direct trauma and dysfunction to the median nerve within the carpal tunnel. The following evidence provides support for the above statements:

a. Different Pathophysiologies

The International Association for the Study of Pain, the most respected international scientific and clinical pain organization, defines and classifies Carpal Tunnel Syndrome as arising from the peripheral nervous system, and not the musculoskeletal system. See Exhibit A, page 127 (which has also been previously submitted and is of record). Accordingly, Carpal Tunnel Syndrome is not a

musculoskeletal disorder, rather it is a neurological or "neuropathic" disorder that results from an entrapment neuropathy (the definition of "neuropathy" is an abnormality in the peripheral nervous system).

Further evidence is presented in Exhibit B from the Mayo Clinic website, which states "The cause of carpal tunnel syndrome is pressure on the median nerve," and Exhibit C, which is an article by Dr. Fuller on the eMedicine website that states: "Symptoms of CTS are a result of median nerve compression at the wrist, with ischemia and impaired axonal transport of the median nerve across the wrist. Compression results from elevated pressures within the carpal canal."

In addition, as reviewed during the Examiner Interview held on April 16, 2007, inflammation of the tenosynovium is not necessary to develop Carpal Tunnel Syndrome. Anything that can result in an increase in pressure within the carpal tunnel and thus cause dysfunction of the median nerve within this area can cause Carpal Tunnel Syndrome. As stated in Exhibit C, "Direct pressure or a space-occupying lesion within the carpal canal can increase pressure on the median nerve and produce CTS. Fracture callus, osteophytes, anomalous muscle bodies, tumors, hypertrophic synovium, gout and other inflammatory conditions, and infection can produce increased pressure within the carpal canal."

Clearly, the pathophysiology of Carpal Tunnel Syndrome differs dramatically from that of sprains, strains, osteoarthritis, rheumatoid arthritis, gout, and alike.

As stated in the Fuller article provided in Exhibit C to this declaration: "Many systemic conditions are strongly associated with CTS. These conditions may directly or indirectly affect microcirculation, pressure thresholds for nerve conduction, nerve cell body synthesis, and axon transport or interstitial fluid pressures. Perturbations in the endocrine system, as observed in individuals with diabetes and hypothyroidism and in women who are pregnant, are linked to CTS. Conditions affecting metabolism (e.g., alcoholism, renal failure with hemodialysis, mucopolysaccharidoses) also are

associated with CTS." And importantly, Dr. Fuller in his eMedicine scientific review article (Exhibit C) writes: "**Inflammation, specifically tenosynovitis, is not part of the pathophysiologic process in chronic idiopathic CTS**." (bolding added for emphasis) Thus, importantly, as stated during the interview, inflammation of the tendon is not necessary to cause the symptoms of Carpal Tunnel Syndrome.

Further evidence is provided in the statement in the Mayo Clinic website (http://www.mayoclinic.com/health/carpal-tunnel-syndrome/DS00326/DSECTION=7) which reads with respect to oral ingestion of NSAIDS: "NSAIDs may help relieve pain from carpal tunnel syndrome if you have an associated inflammatory condition. If no inflammatory condition is involved, NSAIDs are unlikely to help relieve your symptoms." The above statement is only referring to orally administered NSAIDS and is not referring to NSAIDs delivered in any other way.

b. Different Symptomology

Thus, as one would expect, since the underlying pathophysiology of Carpal Tunnel Syndrome is different and distinct than that of musculoskeletal disorders, the symptomatology differs as well.

The type of pain and discomfort experienced by patients experiencing musculoskeletal, or "non-neuropathic" pain, has been shown in many scientific published studies to be different than that experienced by neuropathic pain patients, such as patients suffering from Carpal Tunnel Syndrome. As demonstrated by Dworkin et al, Bennett et al, and Bouhassira et al (see Exhibits D, E, F), patients with peripheral neuropathic pain conditions, which would include Carpal Tunnel Syndrome, describe their symptoms differently than do patients with non-neuropathic pain or musculoskeletal pain, such as patients with osteoarthritis and musculoskeletal back pain. Also, Carpal Tunnel Syndrome patients suffer from other neurological symptoms, such as tingling, numbness, and motor weakness, (Exhibit G) whereas patients suffering from musculoskeletal patients do not.

c. Different Diagnostic Testing

Furthermore, another point of evidence demonstrating the distinction between Carpal Tunnel Syndrome and musculoskeletal disorders is that the Carpal Tunnel Syndrome diagnosis is made with neurological testing, including Nerve Conduction Tests (NCV) and Electromyography (EMG), whereas such testing is not needed for the diagnosis of musculoskeletal disorders, such as sprains, strains, arthritis, and the like (Exhibit H).

d. Different Modes of Pharmacological Action

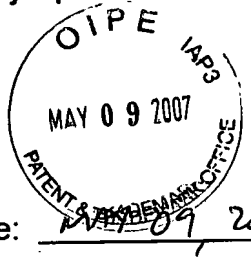
Lastly, as discussed in during the Examiner Interview, the proposed analgesic mechanism of action for the invention is direct activity on the dysfunctional and injured median nerve. As seen in Exhibits I and J, recent scientific animal studies have demonstrated the effectiveness of locally injected (mimicking topical drug delivery) NSAIDs in animal models of nerve injury. Injury to the peripheral nerve results in alterations within the damaged nerve that provide sites for the NSAIDs to be active and provide pain and neuropathic symptom alleviation.

4. The above discussion and supporting exhibits demonstrate that:

- Carpal Tunnel Syndrome has a pathology, symptomatology, and diagnostic testing that is entirely different and distinct from that of the musculoskeletal disorders discussed in Petrus; and

- The pharmacological action of the active agents employed in the claimed methods is entirely different from that which is occurring when NSAIDS are employed to treat musculoskeletal disorders as described in Petrus.

I hereby declare that all statements made herein are of my own knowledge and are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued there from.



Respectfully submitted,

Date: May 09, 2007

By: _____

Bradley Galer

enc:

- Exhibit A- Classification of Chronic Pain, page 127
- Exhibit B- Excerpt from Mayo Clinic Website (http://www.mayoclinic.com/health/carpal-tunnel-syndrome/DS00326/DSECTION=3)
- Exhibit C- Article by Dr. Fuller on the eMedicine website (http://www.emedicine.com/orthoped/topic455.htm)
- Exhibit D- Dworkin et al.
- Exhibit E-Bennett et al.
- Exhibit F-Bouhassira et al.
- Exhibit G-http://www.mayoclinic.com/health/carpal-tunnel-syndrome/DS00326/DSECTION=2
- Exhibit H- Mayo Clinic- http://www.mayoclinic.com/health/carpal-tunnel-syndrome/DS00326/DSECTION=6
- Exhibit I- Guindon J, Beaulieu P.Antihyperalgesic effects of local injections of anandamide, ibuprofen, rofecoxib and their combinations in a model of neuropathic pain. Neuropharmacology. 2006 Jun;50(7):814-23. Epub 2006 Jan 24.
- Exhibit J- Ma W, Eisenach JC. Cyclooxygenase 2 in infiltrating inflammatory cells in injured nerve is universally up-regulated following various types of peripheral nerve injury. Neuroscience. 2003;121(3):691-704.